REMARKS

In this paper, no claim has been amended. Accordingly, no new matter has been introduced.

Claims 1-169 are pending in this application, of which claims 1-3, 161-163, and 169 are pending for further examination on the merits, while claims 4-160, and 164-168 are withdrawn as directed to non-elected subject matter.

Amendment or cancellation of any claim during the prosecution is not to be construed as acquiescence to any of the rejections/objections set forth in the Office Actions, and was done solely to expedite prosecution of this application.

Applicants respectfully reserve the right to pursue any non-elected, cancelled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications. Reconsideration of the application is requested in view of the remarks herein.

Claim Rejection under 35 U.S.C. §103(a)

Claims 1-3, 161-163, and 169 are rejected in the Office Action under 35 U.S.C. §103(a) as allegedly obvious over Yamamoto *et al.* (Chemical & Pharmaceutical Bulletin (1997), 45(8), 1282-1286; hereinafter "Yamamoto"). Applicants strongly disagree and hereby traverse.

To properly determine a *prima facie* case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." *Id.* Three criteria may be helpful in determining whether claimed subject mater is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not

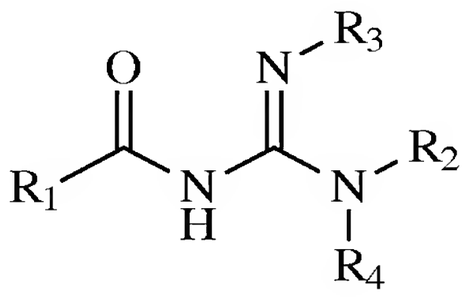
of itself sufficient to render claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

With respect to cases involving new chemical compounds, the Court has taken a long-standing view that

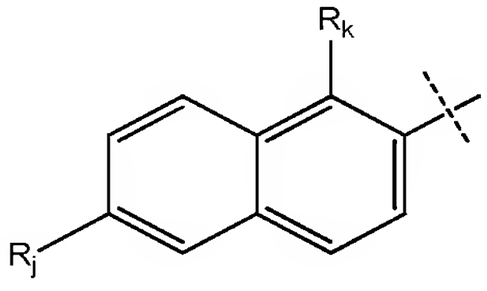
> "Proof of obviousness based on structural similarity [between claimed and prior art compounds] requires **clear and convincing evidence** that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (*e.g.*, a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old." (*Daiichi Sankyo Co. v. Matrix Laboratorories, Ltd.*, 619 F. 3d 1346 (Fed. Cir. 2010); citing *Eisai Co. Ltd. v. Dr. Reddy's Labs, Ltd.* 533 F.3d 1353 (Fed. Cir. 2008), and *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007); emphasis added).

To select a lead compound for further modification, the *Daiichi* court stated that there must be "clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art". 619 F. 3d 1346. Further, the prior art must furnish motivation to one of ordinary skill in the art to modify the lead compound to arrive at the claimed compound. *Id.*

The present invention is directed to an antiviral compound of Formula I, or pharmaceutically acceptable salts thereof,



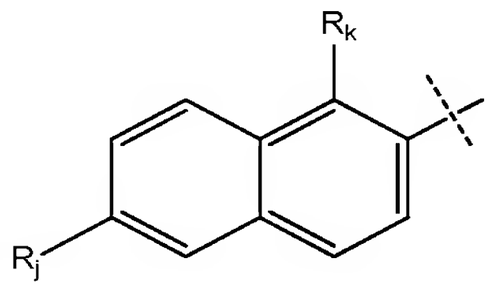
I (*see* claims 1 and 169 for details).

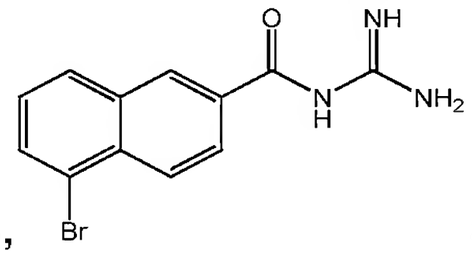
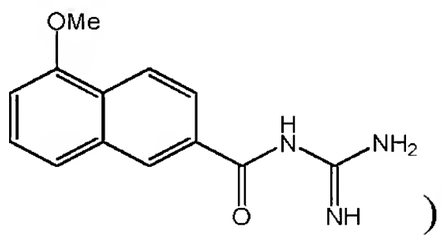
According to the Office, the claimed compounds which share the closest structural similarity are compounds with R_1 being 

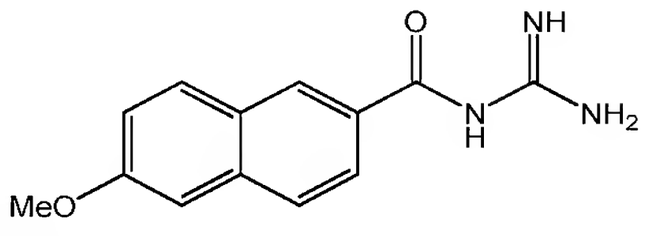
(*see* p. 3-4 of the Office Action). As previously submitted, R_j and R_k in the above R_1 moiety *cannot* be hydrogens at the same time; in addition, R_j *cannot* be a halogen or alkoxy group (*see* claims 1 and

169). As also apparently acknowledged by the Office, Applicants thus submit that Yamamoto does not teach any compounds claimed in the present invention (*see* p. 3-4 of the Office Action).

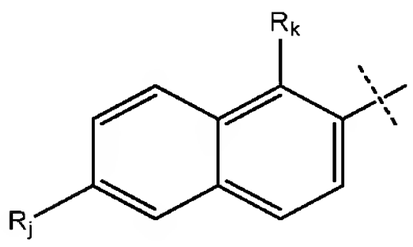
Nevertheless, the Office takes a position that Yamamoto teaches close analogs of the claimed compounds of the present application (p. 3 of the Office Action). The Office then alleges that the claimed compounds are *prima facie* obvious to one skilled in the art as "[p]ositional analogs and adjacent homologs are obvious variants" (see p. 3-4 of the Office Action). Applicants strongly disagree. Applicants respectfully contend that the Office has applied *improper standards* in finding obviousness of the novel compounds (as presently recited and claimed).

Indeed, the Office fails to establish a *prima facie* case of obviousness of the claimed compounds over the Yamamoto disclosure. Applicants submit that the Office does not provide any evidence that one of ordinary skill in the art would have had a reason to select from the Yamamoto disclosure any naphthanyl compound(s) with 1, 2-substituents (when R_j = hydrogen), 2, 6-substituents (when R_k = hydrogen), or 1, 2, 6-substituents (as demonstrated by  in the presently claimed compounds) as the lead compound(s) for further modifications. Moreover, Yamamoto does not present any evidence to one skilled in the art to modify a lead naphthanyl compound on the 1 and/or 6 positions to arrive at the claimed compounds.

By contrast, Yamamoto clearly favors compounds with a substituent at the 5-position of the naphthalene ring, stating "[t]he results indicated that high hydrophobicity of the pseudo-ring moiety and a substituent of appropriate length at the position corresponding to *the 5-position of the naphthalene ring enhance the activity*" (Abstract of Yamamoto; emphasis added). Indeed, among all the compounds it disclosed, Yamamoto strongly favors 5-bromo-2-naphthoylguanidine and 5-methoxy-2-naphthoylguanidine (that is,  and ) over all other compounds (including those having substituents at the 6-position of the naphthalene

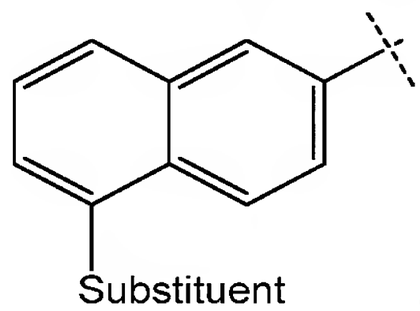
ring, such as, 

)(see Abstract of Yamamoto). In this regard, Yamamoto expressly states that "[a]s expected from the results, 5-bromo-2-naphthoylguanidine 3b and 5-methoxy-2-naphthoylguanidine 3c exhibited strong activity" (Abstract of Yamamoto). Clearly, Yamamoto does not present any motivation for one of ordinary skill in the art to choose a naphthanyl compound bearing



as a lead compound for further modification.

Even assuming, *arguendo,* that a desired naphthanyl compound might be selected from the Yamamoto disclosure as a lead compound, Yamamoto still fails in providing any motivation or suggestion to one skilled in the art to modify the naphthanyl compound at the 1 and/or 6-positions to arrive at the claimed compounds. Rather, in view of the teachings in Yamamoto, one of ordinary skill in the art would pick a

naphthanyl compound with 

as a lead compound for further modifications on its 5-position (as directed by Yamamoto). Accordingly, Applicants submit that Yamamoto, as a whole, explicitly teaches away from the claimed compounds.

Moreover, Applicants note that the compounds disclosed in Yamamoto are designed and tested for their Na/H inhibitory activities. Yamamoto is completely silent with respect to any antiviral activities that its compound may possess. By contrast, the compounds of the present application have demonstrated antiviral activities against viruses from a range of different virus families. Accordingly, Applicants submit that one of skill in the art looking for novel compounds with improved antiviral activity would *not* have any motivation to look to Yamamoto for its teachings on Na/H inhibitors, much less to be motivated to modify the Na/H inhibitory compounds in Yamamoto for the purpose to reach the presently claimed compounds with antiviral activities.

Still further, Applicants respectfully contend that the Office erred in asserting that structurally similar acylguanidines (such as, the so-called "positional analogs" and "adjacent homologs") are anticipated in the art to possess similar properties (p. 4 of the Office Action). Such an assertion is against the common wisdom in the art (i.e., medicinal chemistry). For instance, as both acylguanidines, (2-chlorocinnamoyl)-guanidine and cinnamoylguanidine would be deemed structurally similar in accordance with the Office's views. It follows that one would expect these compounds to have similar properties. Nevertheless, these compounds demonstrate very different patterns on different viral inhibitions. For example, (2-chlorocinnamoyl)guanidine on average is a strong Vpu ion channel blocker as shown by bilayer experiments, and cinnamoylguanidine is a weak Vpu ion channel blocker in the same experiments (*see* Table 3 of Applicants' specification). Interestingly, both of them strongly inhibited the Vpu protein in a bacterial bio-assay (with scores of 4.0 and 2.96 respectively; *see* Table 4 of the specification). Despite their structural similarity, these two acylguanidines have exhibited very different strength and patterns against different biological targets. Accordingly, Applicants submit that the blanket assertion that "structurally similar compounds are anticipated to possess similar properties" set forth in the Office Action is improper and baseless.

In addition, Applicants respectfully submit that the claimed compounds have demonstrated unexpected and surprising pharmacological properties, especially when taken into account of teachings of Yamamoto and the common knowledge in the art. The present inventors have unexpectedly found that the claimed substituted acylguanidines have antiviral activities against viruses from a range of different virus families. For example, certain compounds of the invention exhibit strong inhibitory activities against HIV and/or SARS viruses (*see*, e.g., Tables 5 and 6 of Applicants' specification). In view of Yamamoto's teachings on the use of acylguanidines as the N/H inhibitors, Applicants submit that it is **highly unlikely** for one of ordinary skill in the art to predict these surprising and unexpected antiviral activities demonstrated by the claimed acylguanidines, much less to achieve them with any reasonable expectation of success. Indeed, even assuming, *arguendo*, that one *were* to agree that Yamamoto might establish a *prima facie* showing of obviousness with respect to compound structures, the surprising and unexpected antiviral activities exhibited by the claimed compounds would be sufficient to rebut the *prima facie* showing.

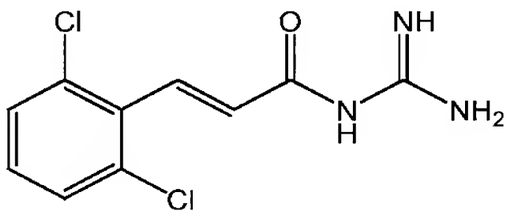
Applicants thus submit that claims 1-3, 161-163, and 169 are patentable over Yamamoto, at least for the following reasons: Yamamoto does not teach or suggest the claimed compounds; Yamamoto fails to supply any clear and convincing evidence that one would be motivated to choose a lead compound having a similar structure to those of the invention for further modifications in order to arrive at the claimed compounds; indeed, Yamamoto explicitly teaches away from the claimed compounds; and, more importantly, there would be no reasonable expectation of success for one of ordinary skill in the art to arrive at the claimed compounds with unexpected antiviral inhibitory activities.

Therefore, reconsideration and withdrawal of the rejection under 35 USC §103(a) of claims 1-3, 161-163, and 169 over Yamamoto is respectfully requested.

Claims 1-3, 161-163, and 169 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Yamamoto in view of Bream (Arzneimittel-Forschung (1975), 25(10), 1477-82; hereinafter "Bream"). The Office asserts that the difference between the prior art compounds and the claimed compounds are "substituents and positional isomerism commonly used in the medicinal chemistry art for optimizing biological properties" (p. 5 of the Office Action). The Office then alleges that the claimed compounds are *prima facie* obvious, as "one of skilled in the art would modify the prior art acylguanidines to arrive at the instantly claim limitations with reasonable expectation of success because Yamamoto *et al.* and Bream teach different acyl groups in acyl guanidine basic pharmacophore provided opportunity for medicinal chemistry effort to arrive at compounds with improved pharmaceutical properties" (p. 5-6 of the Office Action). Applicants strongly disagree and hereby traverse.

Applicants respectfully submit that the claimed subject matter of this application is patentable over Yamamoto, for the reasons delineated above. Applicants further submit that the addition of Bream *does not and cannot* cure any deficiencies of Yamamoto.

Applicants submit that Bream does not teach or suggest any compounds of the present invention. Further, Bream does not furnish any needed motivation or suggestion to one of ordinary skill in the art to combine its teachings with those of Yamamoto to reach the claimed subject matter of this application. Rather, one would not combine Yamamoto and Bream at all, as the compounds of Bream are structurally distinct from those of Yamamoto. As illustration, Bream teaches phenyl compounds (such as,



), while all the compounds taught in Yamamoto have a naphthyl moiety at the left side of their structures *(see* above for the compound structures). In view of this, one of skill in the art would readily recognize that the properties associated with the naphthyl compounds of Yamamoto cannot be attributed, *de facto*, to the phenyl compounds of Bream, or *vice versa*.

Indeed, the compounds of Bream have very different biological activities not only from those of Yamamoto but also from those presently claimed: the phenyl compounds taught in Bream have exhibited good antihypertensive activities, the Yamamoto compounds show N/H inhibitory activities, and the claimed compounds demonstrate good antiviral activities (*see, e.g.,* Abstract for Bream and Abstract for Yamamoto). Accordingly, Applicants contend that one of ordinary skill in the art would not possibly be motivated to extrapolate elements from the prior art compounds, which have distinct structures and also distinct utilities, for combination and modification to reach the claimed compounds with a utility completely distinguishable and different from those taught in the prior art. And the chance in reaching the claimed subject matter with any reasonable expectation of success is even slimmer.

Accordingly, Applicants submit that claims 1, 2, 161-163, and 169 are patentable over Yamamoto in view of Bream, either alone or in combination. Therefore, reconsideration and withdrawal of the rejection under 35 USC § 103(a) over Yamamoto in view of Bream is proper and the same is requested.

CONCLUSIONS

In view of the above amendments and remarks, each of the pending claims in this application is believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be in condition for allowance, the Examiner is requested to call one of Applicant's undersigned representatives to discuss the application. Applicants thank the Examiner in advance for this courtesy.

The Director is hereby authorized to charge any credits or deficiency in the fees filed (or with any paper hereafter filed in the fees filed (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 64681(70403).

Dated: June 6, 2011

Respectfully submitted,

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